

# Hematologic Safety of Radium-223 Dichloride: Baseline Prognostic Factors Associated With Myelosuppression in the ALSYMPCA Trial

Nicholas J. Vogelzang,<sup>1</sup> Robert E. Coleman,<sup>2</sup> Jeff M. Michalski,<sup>3</sup> Sten Nilsson,<sup>4</sup> Joe M. O'Sullivan,<sup>5</sup> Christopher Parker,<sup>6</sup> Anders Widmark,<sup>7</sup> Marcus Thuresson,<sup>8</sup> Lei Xu,<sup>9</sup> Joseph Germino,<sup>10</sup> Oliver Sartor<sup>11</sup>

## Abstract

**Radium-223 was minimally myelosuppressive. Multivariate analyses of data from ALSYMPCA patients identified baseline factors that may increase hematologic toxicity risk with radium-223. Extent of disease and degree of prostate-specific antigen elevation were predictive of grade 2-4 anemia; prior docetaxel, and decreased hemoglobin and platelets were predictive of grade 2-4 thrombocytopenia. Patients with these factors should be closely monitored during radium-223 therapy.**

**Background:** Myelosuppression is common in patients with progressive castration-resistant prostate cancer and bone metastases. Radium-223 prolongs overall survival in these patients but may cause myelosuppression; understanding risk factors will improve clinical decision making. We describe hematologic safety of radium-223 in ALSYMPCA and post hoc analyses identifying patients at increased risk for hematologic toxicity. **Patients and Methods:** Hematologic parameters and adverse events were analyzed. Multivariate analyses assessing baseline risk factors for hematologic toxicities were performed separately for radium-223 and placebo patients. **Results:** Nine hundred one patients received radium-223 (n = 600) or placebo (n = 301); 65% of radium-223 and 48% of placebo patients had the full 6 cycles. Grade 3/4 thrombocytopenia was more common in radium-223 versus placebo patients (6% vs. 2%). Logistic regression analyses identified significant baseline predictors for grade 2-4 hematologic toxicities related to radium-223 treatment: extent of disease (6-20 vs. < 6 bone metastases; odds ratio [OR] = 2.76; P = .022) and elevated prostate-specific antigen (OR = 1.65; P = .006) for anemia; prior docetaxel (OR = 2.16; P = .035), decreased hemoglobin (OR = 1.35; P = .008), and decreased platelets (OR = 1.44; P = .030) for thrombocytopenia. Neutropenia events were too few in placebo patients for a comparative analysis. There were no significant associations between hematologic toxicities and number of radium-223 injections received (4-6 vs. 1-3). **Conclusion:** Radium-223 has a favorable safety profile with a low myelosuppression incidence. Understanding baseline factors associated with myelosuppression may assist clinicians in avoiding severe myelosuppression events with radium-223.

*Clinical Genitourinary Cancer*, Vol. ■, No. ■, 1-11 © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Keywords:** Alpha-emitting radiopharmaceutical, Anemia, Castration-resistant prostate cancer, Myelotoxicity, Thrombocytopenia

Presented in part at the ASCO 2013 Annual Meeting, May 31-June 4, 2013, Chicago, IL; European Cancer Congress 2013 (ECCO-ESMO-ESTRO), September 27-October 1, 2013, Amsterdam, Netherlands; Annual Congress of the European Association of Nuclear Medicine, October 19-23, 2013, Lyon, France; 24th International Prostate Cancer Update, February 19-22, 2014, Vail, CO; and ASTRO's 56th Annual Meeting, September 14-17, 2014, San Francisco, CA.

<sup>1</sup>Comprehensive Cancer Centers of Nevada, Department of Medical Oncology, Las Vegas, NV

<sup>2</sup>Weston Park Hospital, Department of Oncology, Sheffield, UK

<sup>3</sup>Washington University School of Medicine, Radiation Oncology, St Louis, MO

<sup>4</sup>Karolinska University Hospital, Department of Oncology, Stockholm, Sweden

<sup>5</sup>Queen's University, Centre for Cancer Research and Cell Biology, Belfast, UK

<sup>6</sup>Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Academic Urology Unit, Sutton, UK

<sup>7</sup>Umeå University, Department of Radiation Sciences, Umeå, Sweden

<sup>8</sup>Statisticon AB, Biostatistics Department, Uppsala, Sweden

<sup>9</sup>Bayer HealthCare Pharmaceuticals, Global Medical Affairs Oncology, Whippany, NJ

<sup>10</sup>Bayer HealthCare Pharmaceuticals, US Medical Affairs Oncology, Whippany, NJ

<sup>11</sup>Tulane Cancer Center, Departments of Medicine and Urology, New Orleans, LA

Submitted: Jun 6, 2016; Revised: Jul 26, 2016; Accepted: Jul 30, 2016

Address for correspondence: Nicholas J. Vogelzang, MD, Comprehensive Cancer Centers of Nevada, 3730 South Eastern Ave, Las Vegas, NV 89169  
Fax: (702) 952-3453; e-mail contact: [Nicholas.Vogelzang@USOncology.com](mailto:Nicholas.Vogelzang@USOncology.com)

# Safety of Radium-223 in CRPC

## Introduction

More than 90% of men with metastatic castration-resistant prostate cancer (mCRPC) have bone metastases,<sup>1</sup> often with pain and bone fractures.<sup>1-4</sup> Anemia accompanies advancing disease and is a risk factor for poor outcome in mCRPC.<sup>5,6</sup> Docetaxel and cabazitaxel chemotherapy, particularly when given late in the course of the disease, may cause anemia.<sup>7-9</sup> Radium-223 may also cause anemia and thrombocytopenia, which can mimic or exist concurrently with bone marrow failure. Thus, the ability to identify potential risk factors for hematologic toxicity before radium-223 initiation is important, so high-risk patients can be monitored for treatment modifications.

Radium-223 dichloride (radium-223), approved for patients with CRPC and symptomatic bone metastases,<sup>10,11</sup> is a calcium mimetic binding to newly formed bone in areas of bone metastases.<sup>12</sup> The high linear energy transfer of emitted alpha particles causes predominantly nonrepairable double-stranded DNA breaks in tumor cells,<sup>12-14</sup> and the large size of the alpha particle results in a short path length and localized area of intense tissue destruction (< 100  $\mu$ m; 2-10 cell diameters). Unlike beta particle-emitting radionuclides indicated for pain palliation, the short range of therapeutic radium-223 alpha particles spares distant hematologic tissue, which may result in fewer hematologic adverse events (AEs).<sup>13</sup> Early radium-223 experience indicated a low incidence of clinically significant myelosuppression with single injections of up to 250 kBq/kg<sup>15</sup> or 4 doses of 50 kBq/kg (55 kBq/kg following the National Institute of Standards and Technology [NIST] update<sup>16</sup>) over 12 weeks.<sup>17</sup>

ALSYMPCA, a phase III, randomized, double-blind, placebo-controlled multinational study compared efficacy and safety of radium-223 plus best standard of care (BSoC) versus placebo plus BSoC in patients with CRPC and symptomatic bone metastases. Radium-223 significantly improved median overall survival by 3.6 months (hazard ratio [HR] = 0.70; 95% confidence interval, 0.58-0.83;  $P < .001$ ) versus placebo and showed favorable safety with low myelosuppression.<sup>11,18</sup> Based on these results, radium-223 was approved for CRPC patients with symptomatic bone metastases and no visceral metastases.

This report further examines radium-223 hematologic safety in ALSYMPCA, presenting all hematologic AEs with statistical comparisons of select hematologic AEs between treatment groups, detailed post hoc analyses identifying baseline factors that may increase risk for hematologic toxicity, and further characterization of patients who experienced grade 3 or 4 thrombocytopenia and pancytopenia or bone marrow failure.

## Methods

### Patients

ALSYMPCA trial design with full enrollment criteria has been reported.<sup>11</sup> Enrolled patients had symptomatic CRPC and  $\geq 2$  bone metastases with no visceral metastases, elevated and rising prostate-specific antigen (PSA) level, Eastern Cooperative Oncology Group performance status  $\leq 2$ , life expectancy  $\geq 6$  months, and adequate baseline hematologic, renal, and liver function. Adequate hematologic function was defined as absolute neutrophil count  $\geq 1.5 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and hemoglobin  $\geq 10.0$  g/dL. Patients either had previous docetaxel treatment or were

unsuitable for or declined docetaxel. Patients must have had symptomatic disease, ie, requiring regular opioid or nonopioid analgesic use or having received external beam radiation therapy (EBRT) for bone pain within 12 weeks before randomization. Chemotherapy, blood transfusions, and erythropoietin stimulants were not permitted within 4 weeks of randomization; hemibody external radiotherapy and radiopharmaceuticals within 24 weeks were not allowed.

The trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

### Study Design

Patients were randomized 2:1 to radium-223 50 kBq/kg (55 kBq/kg following the NIST update<sup>16</sup>) plus BSoC or placebo plus BSoC every 4 weeks for 24 weeks (6 injections). BSoC was defined as routine care provided at each center and included EBRT for pain as indicated. Patients had received docetaxel or were not healthy enough to receive the drug, they declined it, or it was not available. Data were not collected on the number of previous docetaxel doses or the cumulative docetaxel dose received. Concomitant chemotherapy was not permitted during treatment. The primary end point was overall survival; safety was a secondary end point. The planned follow-up period was 3 years.

### Assessments

Safety was assessed by incidence and severity of hematologic and nonhematologic treatment-emergent AEs, clinical chemistry, electrocardiogram, and physical examination; relationship to treatment was reported as judged by the investigator. All AEs occurring after randomization and within 12 weeks after the last study-drug injection were reported and evaluated for potential relationship to study drug. AEs were graded per Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Grade 3/4 thrombocytopenia was based on investigator's reporting of AEs, which included relevant symptoms, and not based solely on platelet laboratory values.

Blood samples for hematology were to be analyzed in the local laboratory and evaluated within 24 hours before each study-drug administration.

### Statistical Analysis

Statistical methods used in ALSYMPCA have been described.<sup>11,19</sup> Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum values) were presented for clinical laboratory tests (hematology and clinical biochemistry) and their changes from baseline. Post hoc analyses of hematology data included time to first blood transfusion, patients with grade 3 or 4 thrombocytopenia, and patients with preferred term pancytopenia or bone marrow failure. Cox regression analysis was used to assess time to first blood transfusion. Grade 3/4 thrombocytopenia duration was assessed from time of initial recording to resolution, patient death, or close of study database. Fisher's exact test was used to compare hematologic AE rates for radium-223 versus placebo groups, and Wilcoxon rank sum test for differences in laboratory values between groups at different time points.

Post hoc analyses of ALSYMPCA patients treated with radium-223 versus placebo were performed separately using logistic

regression analysis to explore baseline risk factors for grade 2-4 hematologic toxicity; patients with grade 3/4 hematologic toxicity were too few for meaningful analysis. Baseline factors prespecified in ALSYMPCA, including additional baseline covariates based on clinical relevance to the hematologic toxicity, were used in the regression analysis. Baseline factors identified as significantly correlated with grade 2-4 anemia, neutropenia, and thrombocytopenia in the radium-223 subset, but not placebo subset, were considered likely to predict radium-223 treatment effect on AE occurrence. Analyses were performed in 3 steps. First, univariate logistic regression was performed for each potential risk factor. Second, variables with  $P < .10$  in the univariate analysis were entered into the multivariate analysis. Baseline hemoglobin, neutrophils, and platelets were added even if univariate  $P$  was  $> .10$ , given that these factors are expected to correlate with respective hematologic AEs. Third, the model was subject to a stepwise procedure, the optimal model defined as that with the smallest Akaike information criteria (AIC) value.<sup>20</sup> Given the exploratory nature of the analysis, adjustments for multiple comparisons were not made. Statistical programming and analyses used SAS 9.2 (SAS Institute, Cary, NC) and R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria); analyses were based on safety population.

## Results

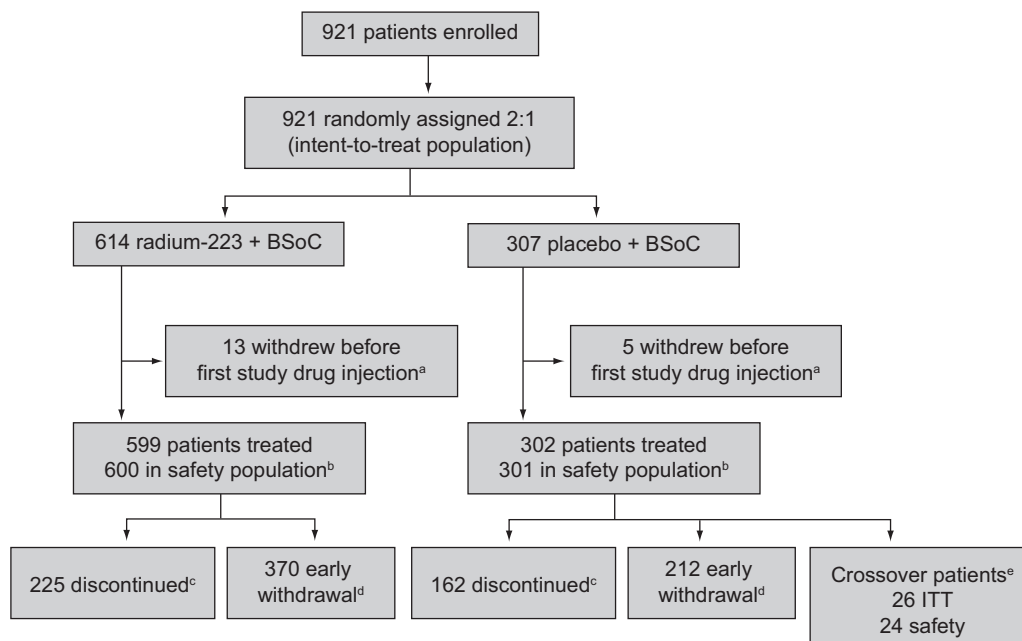
### Patients

ALSYMPCA intent-to-treat (ITT) population included 921 patients randomized to radium-223 plus BSoC or placebo plus BSoC. Safety population included 600 radium-223 and 301 placebo patients who received  $\geq 1$  study-drug injection (Figure 1). Baseline clinical and demographic characteristics were well balanced between groups (Table 1); 387/600 (65%) radium-223 and 145/301 (48%) placebo patients received all 6 study-drug injections (Supplemental Table 1 in the online version).

### Dynamics of Hematologic Laboratory Values

Hemoglobin showed modest decreases in both treatment groups, persisting through follow-up; differences between radium-223 and placebo groups were significant only during follow-up (weeks 44, 51, 69). For radium-223 patients, median hemoglobin decreased from 12.2 g/dL at baseline to 11.4 g/dL at treatment end (week 24) and 10.8 g/dL at follow-up visit 2 (week 44). Among placebo patients, hemoglobin decreased from 12.1 g/dL at baseline to 11.6 g/dL and 11.2 g/dL at weeks 24 and 44, respectively (Figure 2A). Median absolute neutrophil counts (ANCs) decreased modestly in radium-223 patients with some recovery during follow-up. ANC

**Figure 1** CONSORT Flow Chart Indicating Disposition of Patients in ALSYMPCA. <sup>a</sup>Eighteen Patients Were Withdrawn From Study Before First Injection of Study Drug. Additional 2 Patients Received No Treatment and Had Missing Dates of Withdrawal. <sup>b</sup>1 Patient Was Assigned to Placebo but Received Radium-223 at Week 0. This Patient Is Included as Randomly Assigned in ITT Population (Placebo Group) and Is Included in Radium-223 Group for Safety Population. <sup>c</sup>Patients who Discontinued Treatment but Continued to Participate Through Follow-Up Were Not Regarded as Withdrawn From Study. Study Was Ongoing at Time of Data Lock, so Patient Numbers May Not Sum to Total Number Treated. <sup>d</sup>Patients who Withdrew Before Their 3-Year Follow-Up Visit Were Regarded as Having Withdrawn Early From Study. <sup>e</sup>Patients in Placebo Group who Received Treatment With Radium-223 After Study Was Unblinded Were Not Regarded as Having Discontinued Treatment or Withdrawn From Study



Abbreviations: BSoC = best standard of care; ITT = intent to treat.

## Safety of Radium-223 in CRPC

**Table 1** Patient Demographics and Baseline Characteristics (Safety Population; N = 901)

Characteristic <sup>a</sup>	Radium-223 (N = 600)	Placebo (N = 301)
<b>Age</b>		
Median (range), years	71 (49-90)	71 (44-89)
>75 years, n (%)	169 (28)	88 (29)
<b>Race, n (%)</b>		
White	562 (94)	284 (94)
<b>Total Alkaline Phosphatase Level, n (%)</b>		
<220 U/L	345 (58)	165 (55)
≥220 U/L	255 (43)	136 (45)
<b>Current Use of Bisphosphonates at Study Entry, n (%)</b>		
Yes	244 (41)	120 (40)
No	356 (59)	181 (60)
<b>Prior Docetaxel Use, n (%)</b>		
Yes	347 (58)	171 (57)
No	253 (42)	130 (43)
<b>ECOG PS, n (%)<sup>b</sup></b>		
0	162 (27)	77 (26)
1	366 (61)	183 (61)
≥2	72 (12)	40 (13)
<b>WHO Ladder for Cancer Pain, n (%)</b>		
0-1 (no pain or mild pain; no opioid use)	263 (44)	138 (46)
2 (moderate pain; occasional opioid use)	148 (25)	78 (26)
3 (severe pain; regular daily opioid use)	189 (32)	85 (28)
<b>Extent of Disease, n (%)<sup>c</sup></b>		
<6 metastases	100 (16)	38 (12)
6-20 metastases	262 (43)	147 (48)
>20 metastases or superscan <sup>d</sup>	249 (41)	121 (39)
<b>EBRT Within 12 Weeks of Screening, n (%)</b>		
Yes	98 (16)	46 (15)
No	502 (84)	255 (85)
<b>Biochemical Values, Median (Range)<sup>e,f</sup></b>		
Albumin, g/L	40 (24-53)	40 (23-50)
Total alkaline phosphatase, U/L	211 (32-6431)	223 (29-4805)
Lactate dehydrogenase, U/L	315 (76-2171)	336 (132-3856)
Prostate-specific antigen, µg/L	146 (4-6026)	173 (2-14,500)
<b>Hematologic Values, Median (Range)<sup>e,f</sup></b>		
Hemoglobin, g/dL	12.2 (9-16)	12.1 (9-16)
Neutrophils (absolute), ×10 <sup>9</sup> /L	4.5 (1-17)	4.6 (1-14)
Platelets, ×10 <sup>9</sup> /L	244 (69-645)	240 (51-580)
Lymphocytes <sup>g</sup> (absolute), ×10 <sup>9</sup> /L	1.3 (0.3-8)	1.4 (0.1-4)

Abbreviations: EBRT = external beam radiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent to treat; WHO = World Health Organization.

<sup>a</sup>Percentages may not sum to 100% due to rounding.

<sup>b</sup>Value recorded at screening.

<sup>c</sup>Based on the ITT population (radium-223, n = 614; placebo, n = 307).

<sup>d</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>e</sup>Value recorded at week 0. If this value was missing, then the value recorded at screening was used. The normal values were as follows: albumin, 36-45 g/L; total alkaline phosphatase, 35-105 U/L; lactate dehydrogenase, 115-225 U/L; prostate-specific antigen, 0-3.999 µg/L; hemoglobin, 13.4-17.0 g/dL; neutrophils (absolute), 2-7.5 × 10<sup>9</sup>/L; platelets, 150-350 × 10<sup>9</sup>/L; lymphocytes, 1-4 × 10<sup>9</sup>/L.

remained constant for placebo patients, with little change from baseline. Significant differences versus placebo were observed over most of the treatment period: with radium-223, baseline was  $4.5 \times 10^9$ /L; week 24,  $3.3 \times 10^9$ /L; and week 44,  $3.9 \times 10^9$ /L; placebo had corresponding values of  $4.6 \times 10^9$ /L,  $4.5 \times 10^9$ /L, and  $4.3 \times 10^9$ /L, respectively (Figure 2B). Platelet counts for both groups decreased over the treatment period, with larger decreases among radium-223 patients and recovery during follow-up. Between-group platelet count differences were statistically significant over most of the treatment period: with radium-223, baseline was  $244 \times 10^9$ /L, week 24 was  $202 \times 10^9$ /L, and week 44 was  $216 \times 10^9$ /L; placebo had corresponding values of  $240 \times 10^9$ /L,  $232 \times 10^9$ /L, and  $218 \times 10^9$ /L, respectively (Figure 2C).

### Hematologic AEs

No significant differences existed between treatment groups in anemia rates for all grades (radium-223, 31%; placebo, 31%) or grade 3/4 (radium-223, 13%; placebo, 13%). Similarly, grade 3/4 neutropenia rates were not significantly different (radium-223, 2%; placebo, 1%), although significance was reached for all grades (radium-223, 5%; placebo, 1%;  $P = .002$ ). Thrombocytopenia rates reached significance for all-grade (radium-223, 12%; placebo, 6%;  $P = .005$ ) and grade 3/4 events (radium-223, 6%; placebo, 2%;  $P = .005$ ). One patient with grade 5 thrombocytopenia ( $15 \times 10^9$ /L), believed related to radium-223, died from pneumonia with hypoxemia and no evidence of bleeding (Table 2). Additional hematologic AEs observed in ≥ 1 patient with radium-223 treatment are shown in Table 2. Grade 3 febrile neutropenia occurred in 1/600 (< 1%) radium-223 patient and 1/301 (< 1%) placebo patient. One radium-223 patient experienced grade 5 bone marrow failure (hemoglobin 7.0 g/dL, platelets  $53 \times 10^9$ /L, red cells  $2.3 \times 10^{12}$ /mm<sup>3</sup>, leukocytes  $5.8 \times 10^9$ /mm<sup>3</sup>), which the investigator considered not study-drug related; diagnosis was based on laboratory measurements; no bone marrow biopsy was performed. This patient died of prostate cancer with skeletal metastases.

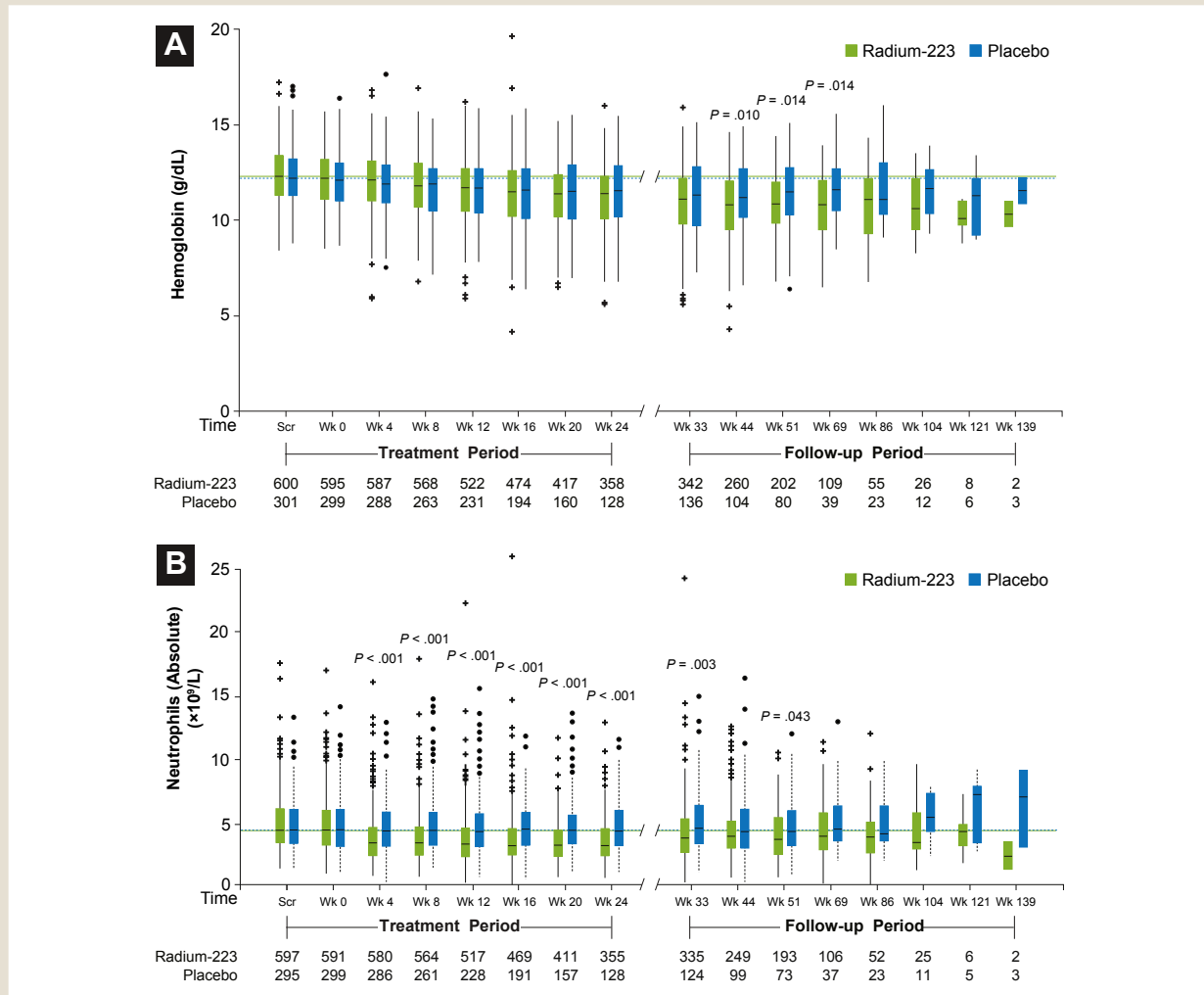
### Blood Transfusions

Similar proportions of radium-223 (42%) and placebo (39%) patients required blood transfusions from randomization to study end. Platelets were more frequently administered to radium-223 patients (Table 3). There was no significant difference between radium-223 and placebo patients in time to first blood transfusion (HR = 0.92; 95% confidence interval, 0.74-1.115;  $P = .452$ ) (Supplemental Figure 1 in the online version).

### Analyses of Baseline Risk Factors for Grade 2-4 Hematologic AEs

Results from univariate and multivariate analyses for radium-223 and placebo patients are shown in Supplemental Tables 2-5 in the online version. Final optimal stepwise models for radium-223 and placebo patients are shown in Table 4 and Supplemental Table 6 in the online version, respectively. Some variables included in the univariate analysis, such as EBRT within 12 weeks of screening, did not reach significance ( $P < .10$ ) as required for inclusion in the multivariate analysis and the stepwise model.

**Figure 2** Box Plots of Hemoglobin (A), Neutrophil (B), and Platelet (C) Values During ALSYMPCA (Safety Population; N = 901). Lower and Upper Boundaries of Boxes Indicate Upper and Lower Quartiles; Horizontal Lines Within Boxes Indicate Medians. Dashed Lines Extend to Extreme Data Points, No More Than 1.5 Times Interquartile Range From Box. More Extreme Data Points Are Identified as Points. Solid Horizontal Line Represents Median Values Obtained at Screening. One Extreme Outlier Was Removed From Radium-223 Week 33 Data ( $> 65 \times 10^9/L$ ) for Neutrophils. *P* Values Are Shown Where Differences Between Median in Radium-223 and Placebo Groups for Individual Time Points Were Significantly Different ( $P \leq .05$ )



The risk-assessment model for grade 2-4 anemia included 169/567 (30%) radium-223 patients and 78/290 (27%) placebo patients with events (Table 4 and Supplemental Table 6 in the online version). Baseline factors significantly associated with increased risk for radium-223 patients were greater extent of disease (6-20 vs.  $< 6$  metastases; odds ratio [OR] = 2.76;  $P = .022$ ) and higher PSA (OR = 1.65;  $P = .006$ ). Risk of grade 2-4 anemia was not statistically significant among those who received 4-6 versus 1-3 radium-223 injections (OR = 1.57;  $P = .097$ ). Baseline factors that were significant in both radium-223 and placebo patients, and therefore not considered risk factors likely to predict radium-223 treatment effect on anemia occurrence, included extent of disease ( $> 20$  vs.  $< 6$  metastases), higher baseline total alkaline phosphatase, and lower baseline hemoglobin levels (Table 4 and Supplemental Table 6 in the online version).

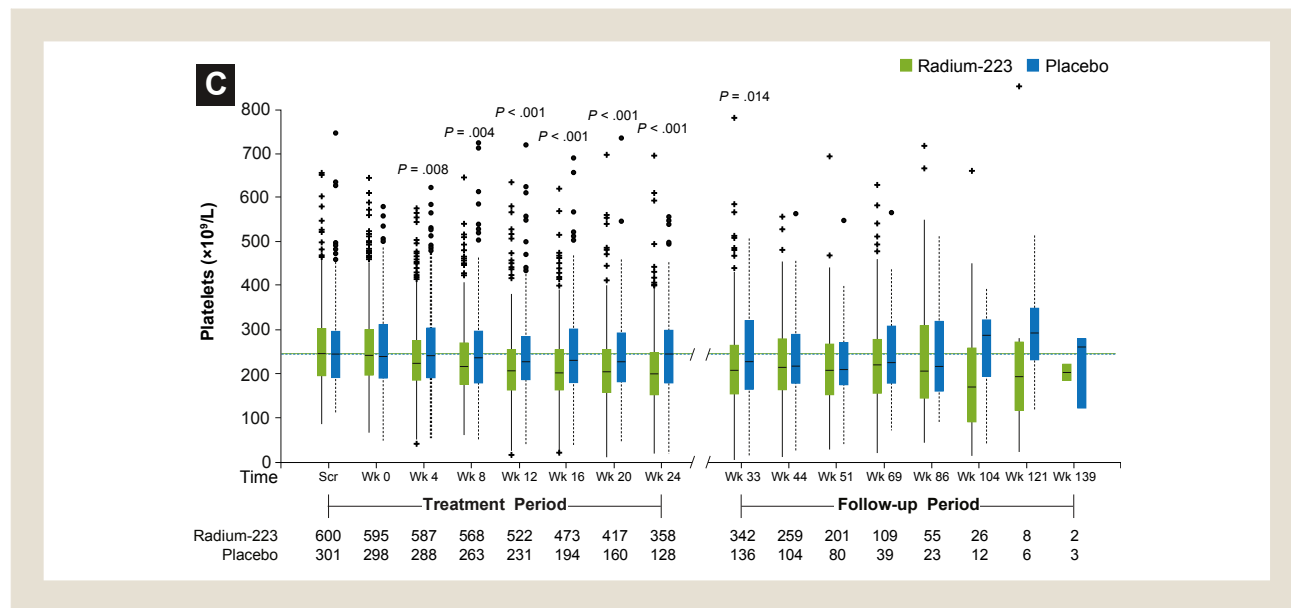
The grade 2-4 neutropenia model included 24/591 (4%) radium-223 patients with events; too few placebo patients (3/301 [1%]) had events for comparative analysis to assess relationship with treatment effect. In radium-223 patients, risk for grade 2-4 neutropenia increased with prior docetaxel therapy (OR = 3.44;  $P = .020$ ), World Health Organization (WHO) ladder cancer pain score (2 vs. 3) (OR = 3.58;  $P = .042$ ), and decrease in baseline neutrophil counts (OR = 2.01;  $P < .001$ ). No significant association existed among radium-223 patients who received 4-6 versus 1-3 radium-223 injections (OR = 1.14;  $P = .837$ ) (Table 4).

The grade 2-4 thrombocytopenia model included 53/573 (9%) radium-223 patients and 11/292 (4%) placebo patients with events (Table 4 and Supplemental Table 6 in the online version). The small number of events among placebo patients reduces confidence in results for this group. Prior docetaxel therapy (OR = 2.16;



## Safety of Radium-223 in CRPC

Figure 2 Continued



Abbreviations: Scr = screening; Wk = week.

$P = .035$ ) and decreases in baseline hemoglobin ( $OR = 1.35$ ;  $P = .008$ ) or platelets ( $OR = 1.44$ ;  $P = .030$ ) were associated with significantly increased risk of grade 2-4 thrombocytopenia among radium-223 patients. Number of radium-223 injections (4-6 vs. 1-3) was not associated with increased risk ( $OR = 0.77$ ;  $P = .475$ ). Baseline factors that were significant in both radium-223 and placebo patients, and therefore not considered risk factors likely to predict radium-223 treatment effect on thrombocytopenia occurrence, included increased age and higher baseline PSA.

### Patients With Grade 3 or 4 Thrombocytopenia

Compared with baseline characteristics of the ALSYMPCA safety population (Table 1), the small group of 38 radium-223 and 6 placebo patients who developed grade 3/4 thrombocytopenia had a higher percentage with prior docetaxel (31/38 [82%] radium-223 and 5/6 [83%] placebo patients) (Supplemental Table 7 in the online version). Other apparent differences included more extensive disease ( $> 20$  metastases or superscan) (23/38 [61%] radium-223 and 3/6 [50%] placebo patients) and higher baseline median PSA (344  $\mu\text{g/L}$  for radium-223 and 1472  $\mu\text{g/L}$  for placebo).

Platelet counts gradually decreased, reaching grade 3/4 at median 19 weeks (range 2.4-38 weeks) relative to first radium-223 injection (Figure 3A); 28/38 patients (74%) received  $\geq 4$ , and 13/38 (34%) received all 6 radium-223 injections. In 9/38 (24%) patients, platelet counts were  $\geq 350 \times 10^9/\text{L}$  at screening; more than half had  $\geq 230 \times 10^9/\text{L}$ . Patients with higher screening platelet counts ( $\geq 223 \times 10^9/\text{L}$ ) and rapid platelet decline during treatment tended to have more advanced disease ( $ALP \geq 220 \text{ U/L}$ ), more bone pain, and more bone metastases (data not shown). Only 1/38 (3%) patient recovered to  $\geq 150 \times 10^9/\text{L}$  with no apparent relationship to screening platelet count. A similar pattern was seen for 6 placebo patients (Figure 3B) with no recovery during follow-up.

The majority of radium-223 patients with grade 3/4 thrombocytopenia (35/38 [92%]) had late onset, after at least the third injection, which may suggest a cumulative effect and mechanism different from that seen with placebo (Figure 3C).

Grade 3/4 thrombocytopenia duration was  $< 4$  weeks for all 6/6 (100%) placebo patients and for 15/38 (39%) radium-223 patients. For 10/38 (26%) radium-223 patients, events had longer duration, 4 to 12 weeks; for 13/38 (34%) patients, duration was  $> 12$  weeks (Figure 3D).

Treatment delays were seen in 16/38 (42%) radium-223 patients with grade 3/4 thrombocytopenia; AEs were the most common reason (14 patients), including anemia ( $n = 5$ ), thrombocytopenia ( $n = 2$ ), neutropenia ( $n = 1$ ), and other AE-related reasons ( $n = 6$ ). Despite treatment delays due to AEs, 6/14 (43%) radium-223 patients completed all 6 injections, including both patients with delay due to grade 3/4 thrombocytopenia.

### Pancytopenia or Bone Marrow Failure

Pancytopenia was reported for 12/600 (2%) radium-223 patients and bone marrow failure for 1/600 ( $< 1\%$ ) radium-223 and no placebo patients. Among 13 radium-223 patients with pancytopenia or bone marrow failure, 5/13 (39%) did not complete all 6 study injections. These 13 patients, versus overall ITT population (Supplemental Table 8 in the online version), show a higher proportion with prior docetaxel exposure (85% vs. 57% respectively) and higher baseline PSA values (344  $\mu\text{g/L}$  vs. 146  $\mu\text{g/L}$ , respectively).

### Discussion

Radium-223 is well tolerated with minimal myelotoxicity in patients with CRPC and bone metastases,<sup>11,15,17,18</sup> comparing well in safety and efficacy with other therapies for these patients.<sup>7,21-24</sup>

**Table 2** Hematologic AEs in ALSYMPCA (Safety Population; N = 901)

Patients With Hematologic AEs, N (%)	Radium-223 (N = 600)					Placebo (N = 301)				
	All Grades	Grade 2	Grade 3	Grade 4	Grade 5 <sup>a</sup>	All Grades	Grade 2	Grade 3	Grade 4	Grade 5 <sup>a</sup>
<b>Hematologic AEs Occurring in ≥5% of Patients</b>										
Anemia	187 (31) <sup>b</sup>	97 (16)	66 (11)	11 (2)	0	92 (31)	44 (15)	37 (12)	2 (1)	1 (<1)
Neutropenia	30 (5)	12 (2)	9 (2)	4 (1)	0	3 (1)	1 (<1)	2 (1)	0	0
Thrombocytopenia	69 (12)	19 (3)	20 (3)	18 (3)	1 (<1)	17 (6)	7 (2)	5 (2)	1 (<1)	0
<b>Additional Hematologic AEs Occurring in ≥1 Radium-223 Patient</b>										
Leukopenia	25 (4)	14 (2)	7 (1)	1 (<1)	0	1 (<1)	0	1 (<1)	0	0
Lymphopenia	5 (1)	2 (<1)	3 (1)	0	0	1 (<1)	0	1 (<1)	0	0
Pancytopenia	12 (2) <sup>b</sup>	4 (1)	4 (1)	3 (1)	0	0	0	0	0	0
AE	P (All Grade AEs) <sup>c</sup>					P (Grade 3 and 4 AEs) <sup>c</sup>				
Anemia	NS					NS				
Neutropenia	.002					NS				
Thrombocytopenia	.005					.005				

Abbreviations: AE = adverse event; NS = not statistically significant ( $P > .05$ ).

<sup>a</sup>Only 1 grade 5 hematologic AE was considered possibly related to the study drug: thrombocytopenia in 1 patient in the radium-223 group who died from pneumonia with hypoxemia, with no evidence of bleeding.

<sup>b</sup>One patient had both a missing and grade 3 AE grade level and is included in N (%). Within a MedDRA system organ class and preferred term, a missing Common Terminology Criteria (CTC) grade is taken as the "worst" case unless the nonmissing CTC grade is 5; then the maximum toxicity is CTC grade 5.

<sup>c</sup>P values were calculated from Fisher's exact tests comparing the AE rates between radium-223 and placebo groups.

Table 3 Incidence of Blood Transfusions (ITT Population; N = 921)									
Treatment	No. (%) of Patients With Blood Transfusion <sup>a</sup>						Between End of Treatment and End of Study <sup>b</sup>		
	Between Randomization and End of Treatment <sup>c</sup>			Between End of Treatment and End of Study <sup>b</sup>			Between End of Treatment and End of Study <sup>b</sup>		
	Total	Whole Blood or RBC	Platelets	Missing	Total	Whole Blood or RBC	Platelets	Missing	Missing
Radium-223 (n = 614)	256 (42)	252 (41)	26 (4)	6 (1)	137 (22)	136 (22)	6 (1)	3 (1)	195 (32)
Placebo (n = 307)	119 (39)	118 (38)	2 (1)	2 (1)	69 (23)	68 (22)	0	2 (1)	80 (26)
									2 (1)
									0

Abbreviations: ITT = intent to treat; RBC = red blood cells.

<sup>a</sup>If it was unclear during which time period the transfusion occurred, the earliest postrandomization time period was assumed.

<sup>b</sup>End of study refers to when the patient is withdrawn, died, or completed the 3-year follow-up visit.

<sup>c</sup>End of treatment was defined as 4 weeks after the last study-drug injection.

Although there were no significant associations between hematologic toxicities and number of radium-223 injections received, it is important to note that patients were supported with transfusions as needed and as described in the prescribing information.<sup>10</sup> A high rate of anemia in patients with CRPC and bone metastases has been reported.<sup>5,6</sup> In ALSYMPCA, anemia was the most common hematologic toxicity; its frequency and severity were the same with radium-223 and placebo and likely due to disease burden, although concomitant BSoC treatment effects were not accounted for. Median baseline values for hemoglobin ( $\approx 12$  g/dL) suggest that many or most patients were anemic at study entry, and logistic regression analysis showed correlations between grade 2-4 anemia and factors related to extent of disease (eg, elevated PSA and higher extent of disease) in radium-223 patients. Current prescribing information recommends that hemoglobin be  $\geq 10$  g/dL prior to first radium-223 administration. Ongoing protocols allow hemoglobin  $\geq 8$  g/dL (with transfusions).

Neutropenia was more common in radium-223 patients. Neutrophil counts decreased with radium-223 treatment, but grade 3/4 events were rare and too few with placebo for comparison to assess the relationship with treatment effect in the logistic regression analysis.

Thrombocytopenia was more common in radium-223 patients, and risk increased with prior docetaxel and decreased baseline hemoglobin and platelets. Its association with prior docetaxel use is consistent with earlier analysis of ALSYMPCA patients showing a 3-fold greater incidence of grade 3/4 thrombocytopenia among radium-223 patients previously exposed to docetaxel versus those not exposed (9% vs. 3%).<sup>25</sup> Prudent management requires blood count evaluation before each radium-223 dose, with minimum values defined as a threshold for continued treatment, per current prescribing information (Supplemental Table 9 in the online version).<sup>10</sup> Prior to the first injection, ANC should be  $\geq 1.5 \times 10^9/L$  and platelets should be  $\geq 100 \times 10^9/L$ . Prior to each subsequent injection, ANC should be  $\geq 1.0 \times 10^9/L$  and platelets should be  $\geq 50 \times 10^9/L$ . If there is no recovery to these values within 6 to 8 weeks after the last injection despite supportive care, radium-223 should be discontinued.

No differences between radium-223 and placebo groups exists in frequency of blood transfusions or time to first blood transfusion, a finding that is noteworthy in this mCRPC population.

Clinicians are advised to balance benefit and risk when determining whether to continue treatment. It is acceptable to delay treatment; delays allowing completion of 6 radium-223 cycles may be key to ensuring maximum treatment benefit. It is important to note that thrombocytopenia onset was slow and did not warrant abrupt discontinuation of radium-223, and that number of radium-223 doses was not a risk factor in thrombocytopenia development.

Current treatment guidelines for CRPC and bone metastases recommend radium-223 as a first-line option in predocetaxel and postdocetaxel settings.<sup>26-29</sup> Analysis of outcomes for ALSYMPCA patients who received chemotherapy ( $\sim 70\%$  of which was docetaxel) after completing the study-drug regimen (radium-223 or placebo) identified no new hematologic concerns and no



**Table 4** Stepwise Analysis of Grade 2-4 Anemia, Neutropenia, and Thrombocytopenia (Radium-223, Safety Population; N = 600)

Baseline Variable	Anemia (N = 567)		Neutropenia (N = 591)		Thrombocytopenia (N = 573)	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
4-6 injections vs. 1-3 injections	1.57 (0.92-2.69)	.097	1.14 (0.32-4.12)	.837	0.77 (0.38-1.56)	.475
Age (years) per 1-year increase <sup>a</sup>					0.96 (0.92-0.99)	.025
<b>Extent of Disease</b>						
6-20 metastases vs. <6 metastases	2.76 (1.16-6.57)	.022				
>20 metastases vs. <6 metastases	2.78 (1.14-6.78)	.025				
Superscan <sup>b</sup> vs. <6 metastases	2.55 (0.86-7.58)	.093				
Log baseline tALP per 10-fold increase <sup>c</sup>	2.00 (1.12-3.55)	.019				
Log baseline PSA per 10-fold increase <sup>c</sup>	1.65 (1.15-2.36)	.006			1.83 (1.12-2.99)	.016
Prior docetaxel use (yes/no)	1.49 (0.96-2.30)	.077	3.44 (1.21-9.74)	.020	2.16 (1.06-4.42)	.035
<b>WHO Ladder for Cancer Pain<sup>d</sup></b>						
1 vs. 3			1.50 (0.44-5.13)	.522		
2 vs. 3			3.58 (1.05-12.22)	.042		
Baseline hemoglobin per 1 unit decrease	1.84 (1.55-2.19)	<.001			1.35 (1.08-1.68)	.008
Baseline neutrophil per 1 unit decrease			2.01 (1.41-2.87)	<.001		
Baseline platelet per 100 unit decrease					1.44 (1.04-2.00)	.030

Based on a logistic regression model. Odds ratios of > 1 represent an increase in risk associated with an increase in baseline variable. Odds ratios are relative risk for 1 unit increase in baseline variable (for those without log transformation) or a 10-times increase (for those with log transformation).

Abbreviations: N = number of radium-223 and placebo patients included in the model; PSA = prostate-specific antigen; tALP = total alkaline phosphatase; WHO = World Health Organization.

<sup>a</sup>Relative increase in risk for an adverse event with respect to an increase in age of 1 year.

<sup>b</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>c</sup>Log transformation was performed for baseline variables with heavily skewed distributions. A WHO ladder score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use.

<sup>d</sup>Analysis includes 12 patients in the radium-223 group and 2 patients in the placebo group with no pain or analgesic use at baseline.

detrimental effects of prior radium-223 on overall survival.<sup>30</sup> Given these findings and those of current analyses regarding the relationship of radium-223 and prior docetaxel exposure to thrombocytopenia development, it may be prudent to consider radium-223 prior to docetaxel, although close monitoring of hematologic parameters may be required for patients who receive chemotherapy later in the treatment sequence.

## Conclusion

Hematologic AEs are manageable if recognized early and handled with appropriate care, generally allowing continued treatment for maximum benefit. These ALSYMPCA data provide guidance to clinicians and help place their clinical experience with radium-223 into a broader context. Following recommendations in the prescribing information,<sup>10</sup> with insights from the current analysis, may enhance appropriate patient management and safety.

## Clinical Practice Points

- In the phase III ALSYMPCA trial, radium-223 significantly improved overall survival and delayed time to first symptomatic skeletal event with a favorable safety profile, leading to its approval for the treatment of patients with CRPC and symptomatic bone metastases and no visceral metastases
- Overall, radium-223 was well tolerated and had a favorable hematologic safety profile with a low incidence of myelosuppression

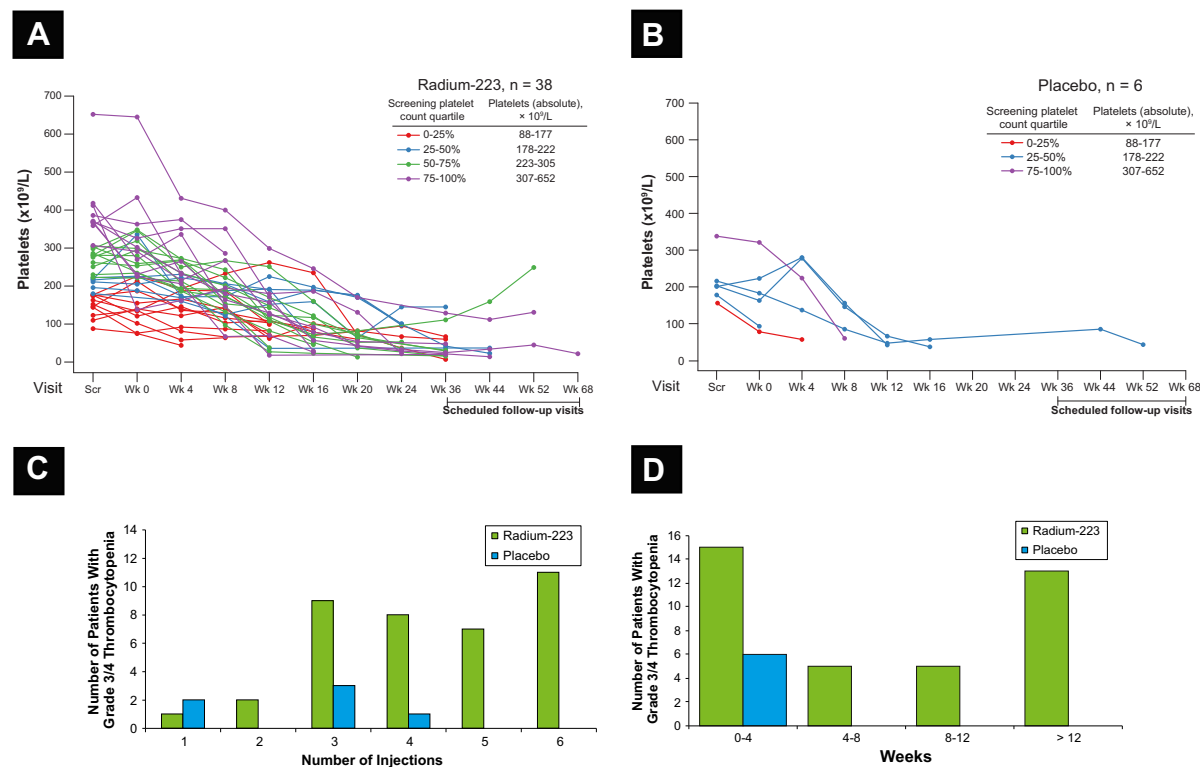
- Post hoc analyses identified baseline risk factors associated with hematologic toxicities related to radium-223 treatment; prior docetaxel therapy and decreased platelet and hemoglobin levels were risk factors for grade 2-4 thrombocytopenia, and baseline extent of disease (6-20 vs. < 6 bone metastases) and elevated PSA were risk factors for grade 2-4 anemia; neutropenia events in placebo patients were too few for a comparative analysis to assess a relationship with treatment effect
- These baseline factors and thrombocytopenia occurrence are clinical considerations important for patient management
- Insights provided in this post hoc analysis can serve as a guide for clinicians to help carefully examine risk factors that may predict hematologic toxicities and identify high-risk patients who may benefit from close monitoring
- The favorable safety profile and unique mechanism of action of radium-223 suggest that it is suitable for use in combination or sequentially with other agents

## Acknowledgments

Funding for ALSYMPCA was provided by Bayer AS (formerly Algeta ASA) and Bayer HealthCare Pharmaceuticals. Funding for manuscript development was provided by Bayer HealthCare Pharmaceuticals. Medical writing and editorial assistance was provided by Julia D'Ambrosio, PhD, and Richard McCabe, PhD, of SciStrategy Communications, funded by Bayer HealthCare Pharmaceuticals.

## Safety of Radium-223 in CRPC

**Figure 3** Patients With Grade 3 or 4 Thrombocytopenia. Quartile Distribution of Platelet Counts Over Time Based on Platelet Counts at Screening for Patients Receiving Radium-223 (A) or Placebo (B); Time to Onset of Grade 3/4 Thrombocytopenia (C) by Number of Injections of Radium-223 or Placebo Received Before Onset, and Duration of Thrombocytopenia (D) by Time (Weeks) Since First Dose of Radium-223 or Placebo



## Disclosure

N.J.V. has served as a consultant for Bayer, Genentech, Exelixis, Medivation, and Pfizer, and has served on speakers bureaus for BMS, Pfizer, Genentech, Novartis, Sanofi Aventis, Dendreon, and Bayer. R.E.C. has received grants or funding to his institution from Bayer, Amgen, and Celgene. J.M.M. has no conflicts of interest to disclose. S.N. has served as a consultant or advisor for Bayer. J.M.O. has received grants or funding from Bayer and has served as a consultant or advisor for and on the speakers bureaus for Astellas, Bayer, Sanofi, and Janssen. C.P. has received grants or funding from Bayer and honoraria from Bayer and Janssen. A.W. has received honoraria from and served as a consultant or advisor for Sanofi, Astellas, EXINI, and Roche, and has received travel, accommodations, or expenses from Sanofi and Astellas. M.T. has served as a consultant or advisor for Bayer. L.X. and J.G. are employed by Bayer HealthCare Pharmaceuticals. O.S. has received grants or funding from, served as a consultant or advisor for, and received honoraria from Bayer.

## Supplemental Data

Supplemental tables and figure accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clgc.2016.07.027>.

## References

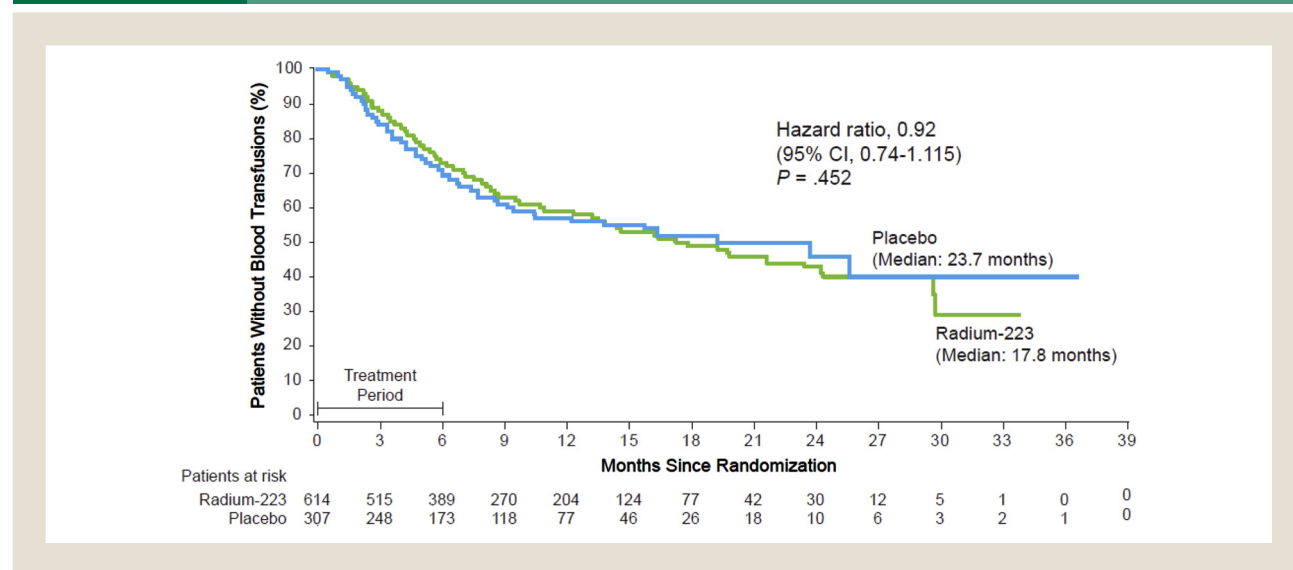
- Gartrell BA, Saad F. Managing bone metastases and reducing skeletal related events in prostate cancer. *Nat Rev Clin Oncol* 2014; 11:335-45.
- Cathomas R, Bajory Z, Bouzid M, et al. Management of bone metastases in patients with castration-resistant prostate cancer. *Urol Int* 2014; 92:377-86.
- Butoescu V, Tombal B. Practical guide to bone health in the spectrum of advanced prostate cancer. *Can J Urol* 2014; 21:84-92.
- Broder MS, Gutierrez B, Cherepanov D, et al. Burden of skeletal-related events in prostate cancer: unmet need in pain improvement. *Support Care Cancer* 2015; 23: 237-47.
- Nieder C, Haukland E, Pawinski A, et al. Anaemia and thrombocytopenia in patients with prostate cancer and bone metastases. *BMC Cancer* 2010; 10:284.
- Beer TM, Bergenstock M, Birt K, et al. Darbepoetin alfa administered every 4 weeks for anemia in patients with advanced prostate cancer. *Clin Genitourin Cancer* 2007; 5:329-33.
- Picus J, Schultz M. Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. *Semin Oncol* 1999; 26: 14-8.

8. Hwang C. Overcoming docetaxel resistance in prostate cancer: a perspective review. *Ther Adv Med Oncol* 2012; 4:329-40.
9. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; 376:1147-54.
10. *Xofigo (Radium-223 Dichloride) [Package Insert]*. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; 2013.
11. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369:213-23.
12. Bruland OS, Nilsson S, Fisher DR, et al. High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter  $^{223}\text{Ra}$ : adjuvant or alternative to conventional modalities? *Clin Cancer Res* 2006; 12:6250s-7s.
13. Henriksen G, Fisher DR, Roeske JC, et al. Targeting of osseous sites with alpha-emitting  $^{223}\text{Ra}$ : comparison with the beta-emitter  $^{89}\text{Sr}$  in mice. *J Nucl Med* 2003; 44:252-9.
14. Henriksen G, Bristol K, Bruland OS, et al. Significant antitumor effect from bone-seeking, alpha-particle-emitting  $^{223}\text{Ra}$  demonstrated in an experimental skeletal metastases model. *Cancer Res* 2002; 62:3120-5.
15. Nilsson S, Larsen RH, Fossa SD, et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. *Clin Cancer Res* 2005; 11:4451-9.
16. Zimmerman BE, Bergeron DE, Cessna JT, et al. Revision of the NIST standard for  $^{223}\text{Ra}$ : new measurements and review of 2008 data. *J Res Natl Inst Stand Technol* 2015; 120:37-57.
17. Nilsson S, Franzen L, Parker C, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. *Lancet Oncol* 2007; 8:587-94.
18. Nilsson S. Radium-223 dichloride for the treatment of bone metastatic castration-resistant prostate cancer: an evaluation of its safety. *Expert Opin Drug Saf* 2015; 14: 1127-36.
19. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol* 2014; 15:738-46.
20. Therneau TM, Grambsch PM, Pankratz VS. Penalized survival models and frailty. *J Comput Graph Stat* 2003; 12:156-75.
21. *Provenge (Sipuleucel-T) Suspension for Intravenous Infusion [Package Insert]*. Seattle, WA: Dendreon Corporation; 2014.
22. *Jetavana (Cabazitaxel) Injection, 60 mg/1.5 mL, for Intravenous Infusion Only [Package Insert]*. Bridgewater, NJ: Sanofi-Aventis US LLC; 2014.
23. *Zytiga (Abiraterone Acetate) Tablets for Oral Administration [Package Insert]*. Horsham, PA: Janssen Biotech Inc; 2014.
24. *Xtandi (Enzalutamide) Capsules for Oral Use [Package Insert]*. Northbrook, IL: Astellas Pharma US Inc; 2014.
25. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol* 2014; 15:1397-406.
26. Cookson S, Roth BJ, Dahm P, et al. *Castration-Resistant Prostate Cancer: AUA Guideline*. Linthicum, MD: AUA Education and Research Inc; 2014.
27. Omlin A, Pezaro C, Gillessen Sommer S. Sequential use of novel therapeutics in advanced prostate cancer following docetaxel chemotherapy. *Ther Adv Urol* 2014; 6:3-14.
28. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *J Clin Oncol* 2014; 32:3436-48.
29. Parker C, Gillessen S, Heidenreich A, et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26(suppl 5):v69-77.
30. Sartor O, Hoskin P, Coleman RE, et al. Chemotherapy following radium-223 dichloride treatment in ALSYMPCA. *Prostate* 2016; 76:905-16.

## Safety of Radium-223 in CRPC

**Supplemental Table 1** Number of Study-Drug Injections Received by Patients in ALSYMPCA (Safety Population; N = 901)

No. of Study-Drug Injections	No. (%) Patients With:	
	Radium-223 (N = 600)	Placebo (N = 301)
1	18 (3)	21 (7)
2	37 (6)	36 (12)
3	48 (8)	37 (12)
4	60 (10)	34 (11)
5	49 (8)	29 (10)
6	387 (65)	145 (48)

**Supplemental Figure 1** Time to First Blood Transfusion (Intent-to-Treat Population; N = 921)

Abbreviations: CI = confidence interval; HR = hazard ratio.

**Supplemental Table 2** Univariate Analysis of Grades 2-4 Anemia, Neutropenia, and Thrombocytopenia (Radium-223, Safety Population; N = 600)

Baseline Variable	Anemia (N = 567)			Neutropenia (N = 591)			Thrombocytopenia (N = 573)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age <sup>a,b</sup> (years) per 1-year increase	0.99	0.97-1.01	.224	0.96	0.91-1.01	.103	0.96	0.93-1.00	.033
Prior docetaxel use (yes/no)	1.63	1.13-2.37	.009	3.03	1.21-9.21	.029	3.01	1.61-6.08	.001
Current use of bisphosphonates (yes/no)	1.32	0.92-1.89	.126	0.96	0.41-2.16	.930	1.60	0.92-2.78	.092
<b>ECOG PS<sup>b</sup></b>									
1 vs. 0	1.46	0.96-2.26	.080	1.66	0.65-5.11	.325	0.87	0.48-1.64	.653
>2 vs. 0	1.40	0.75-2.61	.287	0.95	0.13-4.58	.956	0.57	0.18-1.54	.300
<b>Extent of Disease<sup>b</sup></b>									
6-20 metastases vs. <6 metastases	5.35	2.52-13.22	<.001	0.95	0.34-3.07	.930	3.18	1.08-13.64	.064
>20 metastases vs. <6 metastases	7.22	3.37-17.97	<.001	0.74	0.23-2.56	.611	4.16	1.40-17.91	.023
Superscan <sup>c</sup> vs. <6 metastases	12.70	5.14-35.10	<.001	0.40	0.02-2.63	.416	4.66	1.22-22.56	.032
<b>External Beam Radiotherapy</b>									
<12 weeks of screening (yes/no)	1.04	0.73-1.48	.830	1.12	0.50-2.54	.781	1.06	0.61-1.85	.844
<b>WHO Ladder for Cancer Pain<sup>b,d</sup></b>									
1 vs. 3	0.53	0.35-0.79	.002	1.78	0.58-6.60	.336	0.54	0.29-0.99	.049
2 vs. 3	0.57	0.35-0.91	.019	3.60	1.20-13.28	.032	0.53	0.24-1.09	.094
Log baseline tALP per 10-fold increase <sup>e</sup>	5.56	3.50-9.00	<.001	1.17	0.43-3.02	.758	1.91	0.99-3.65	.051
Log baseline LDH per 10-fold increase <sup>b,e</sup>	8.07	3.68-18.08	<.001	0.89	0.14-5.03	.902	1.36	0.41-4.30	.612
Log baseline PSA per 10-fold increase <sup>b,e</sup>	2.58	1.91-3.54	<.001	1.48	0.78-2.82	.232	2.22	1.42-3.54	.001
Baseline albumin <sup>b</sup> per 1 unit decrease	1.07	1.03-1.12	<.001	1.00	0.92-1.09	.950	1.03	0.97-1.09	.359
Baseline hemoglobin <sup>b</sup> per 1 unit decrease	2.12	1.82-2.50	<.001	1.07	0.81-1.42	.626	1.36	1.12-1.66	.002
Baseline neutrophil <sup>b</sup> per 1 unit decrease	0.96	0.89-1.04	.343	2.17	1.55-3.22	<.001	1.09	0.95-1.26	.248
Baseline platelet <sup>b</sup> per 100 unit decrease	0.79	0.65-0.95	.015	1.17	0.75-1.96	.513	1.20	0.87-1.69	.283

Based on a logistic regression model. Odds ratios of > 1 represent an increase in risk associated with an increase in baseline variable. Odds ratios are relative risk for 1 unit increase in baseline variable (for those without log transformation) or a 10-times increase (for those with log transformation). Analyses include adjustment for treatment effect.

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; N = number of patients included in the model; OR = odds ratio; PSA = prostate-specific antigen; tALP = total alkaline phosphatase; WHO = World Health Organization.

<sup>a</sup>Relative increase in risk for an adverse event with respect to an increase in age of 1 year.

<sup>b</sup>ALSYMPCA was not randomized by age, ECOG PS, extent of disease, WHO pain score subgroups, LDH, PSA, albumin, hemoglobin, or neutrophil or platelet counts, and results may be due to chance.

<sup>c</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>d</sup>Analysis includes 12 patients in the radium-223 group with no pain or analgesic use at baseline. A WHO ladder score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use.

<sup>e</sup>Log transformation was performed for baseline variables with heavily skewed distributions.



**Supplemental Table 3** Multivariate Analysis of Grades 2-4 Anemia, Neutropenia, and Thrombocytopenia (Radium-223, Safety Population; N = 600)

Baseline Variable	Anemia (N = 567)			Neutropenia (N = 591)			Thrombocytopenia (N = 573)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
4-6 injections vs. 1-3 injections	1.64	0.94-2.86	.080	1.14	0.32-4.12	0.837	0.82	0.40-1.67	.590
Age <sup>a,b</sup> (years) per 1-year increase							0.96	0.92-1.00	.033
Prior docetaxel use (yes/no)	1.39	0.88-2.18	.157	3.44	1.21-9.74	.020	1.98	0.96-4.11	.066
Current use of bisphosphonates (yes/no)							1.41	0.77-2.58	.271
<b>Extent of Disease<sup>b</sup></b>									
6-20 metastases vs. <6 metastases	2.75	1.15-6.58	.023				3.30	0.73-14.82	.119
>20 metastases vs. <6 metastases	2.73	1.11-6.71	.029				2.87	0.62-13.26	.178
Superscan <sup>c</sup> vs. <6 metastases	2.63	0.87-7.96	.087				2.02	0.35-11.71	.432
<b>WHO Ladder for Cancer Pain<sup>b,d</sup></b>									
1 vs. 3	0.74	0.46-1.22	.238	1.50	0.44-5.13	.522	0.65	0.33-1.29	.217
2 vs. 3	0.72	0.41-1.27	.255	3.58	1.05-12.22	.042	0.64	0.28-1.45	.280
Log baseline tALP per 10-fold increase <sup>e</sup>	1.89	1.03-3.47	.041				1.12	0.48-2.61	.794
Log baseline LDH per 10-fold increase <sup>b,e</sup>	1.31	0.49-3.48	.592						
Log baseline PSA per 10-fold increase <sup>b,e</sup>	1.63	1.13-2.34	.008				1.81	1.09-3.00	.022
Baseline albumin <sup>b</sup> per 1 unit decrease	0.99	0.95-1.04	.829						
Baseline hemoglobin <sup>b</sup> per 1 unit decrease	1.81	1.51-2.17	<.001				1.30	1.02-1.66	.032
Baseline neutrophil <sup>b</sup> per 1 unit decrease				2.01	1.41-2.87	<.001			
Baseline platelet <sup>b</sup> per 100 unit decrease	0.92	0.74-1.16	.494				1.53	1.07-2.17	.019

Based on a logistic regression model. Odds ratios of > 1 represent an increase in risk associated with an increase in baseline variable. Odds ratios are relative risk for 1 unit increase in baseline variable (for those without log transformation) or a 10-times increase (for those with log transformation). Analyses include adjustment for treatment effect.

Abbreviations: LDH = lactate dehydrogenase; N = number of patients included in the model; OR = odds ratio; PSA = prostate-specific antigen; tALP = total alkaline phosphatase; WHO = World Health Organization.

<sup>a</sup>Relative increase in risk for an adverse event with respect to an increase in age of 1 year.

<sup>b</sup>ALSYMPCA was not randomized by age, extent of disease, WHO pain score subgroups, LDH, PSA, albumin, hemoglobin, or neutrophil or platelet counts, and results may be due to chance.

<sup>c</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>d</sup>Analysis includes 12 patients in the radium-223 group with no pain or analgesic use at baseline. A WHO ladder score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use.

<sup>e</sup>Log transformation was performed for baseline variables with heavily skewed distributions.

**Supplemental Table 4** Univariate Analysis of Grades 2-4 Anemia and Thrombocytopenia (Placebo Patients, Safety Population; N = 301)<sup>a</sup>

Baseline Variable	Anemia (N = 290)			Thrombocytopenia (N = 292)		
	OR	95% CI	P	OR	95% CI	P
Age (years) <sup>b,c</sup> per 1-year increase	0.96	0.93-0.99	.023	0.93	0.86-0.99	.037
Prior docetaxel use (yes/no)	1.73	1.03-2.95	.042	2.63	0.79-11.91	.148
Current use of bisphosphonates (yes/no)	0.93	0.55-1.55	.774	0.94	0.28-2.89	.916
<b>ECOG PS<sup>c</sup></b>						
1 vs. 0	1.60	0.86-3.09	.149	0.98	0.26-4.65	.978
≥2 vs. 0	1.84	0.77-4.35	.167	1.30	0.17-8.15	.780
<b>Extent of Disease<sup>c</sup></b>						
6-20 metastases vs. <6 metastases	4.57	1.29-29.10	.044			
>20 metastases vs. <6 metastases	11.02	3.08-70.58	.002			
Superscan <sup>d</sup> vs. <6 metastases	20.00	4.87-137.56	<.001			
<b>External Beam Radiotherapy</b>						
≤12 weeks of screening (yes/no)	0.89	0.54-1.48	.659	0.93	0.29-2.87	.901
<b>WHO Ladder for Cancer Pain<sup>e,g</sup></b>						
1 vs. 3	0.66	0.36-1.19	.162	0.60	0.14-2.62	.485
2 vs. 3	0.62	0.31-1.23	.174	1.39	0.35-5.79	.635
Log baseline tALP per 10-fold increase <sup>f</sup>	6.26	3.20-12.81	<.001	1.18	0.29-4.41	.812
Log baseline LDH per 10-fold increase <sup>e,f</sup>	2.54	0.96-6.75	.060	2.13	0.24-14.14	.459
Log baseline PSA per 10-fold increase <sup>e,f</sup>	2.40	1.58-3.74	<.001	8.46	2.87-29.88	<.001
Baseline albumin <sup>c</sup> per 1 unit decrease	1.03	0.98-1.09	.283	1.00	0.88-1.12	.967
Baseline hemoglobin <sup>c</sup> per 1 unit decrease	1.71	1.40-2.10	<.001	1.10	0.75-1.65	.624
Baseline neutrophil <sup>c</sup> per 1 unit decrease	1.01	0.90-1.15	.864	0.87	0.69-1.14	.273
Baseline platelet <sup>c</sup> per 100 unit decrease	0.75	0.57-0.99	.040	1.76	0.87-3.99	.148

Based on a logistic regression model. Odds ratios of > 1 represent an increase in risk associated with an increase in baseline variable. Odds ratios are relative risk for 1 unit increase in baseline variable (for those without log transformation) or a 10-times increase (for those with log transformation). Analyses include adjustment for treatment effect.

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; N = number of patients included in the model; OR = odds ratio; PSA = prostate-specific antigen; tALP = total alkaline phosphatase; WHO = World Health Organization.

<sup>a</sup>There were too few placebo patients with events for any valid analysis.

<sup>b</sup>Relative increase in risk for an adverse event with respect to an increase in age of 1 year.

<sup>c</sup>ALSYMPCA was not randomized by age, ECOG PS, extent of disease, WHO pain score subgroups, LDH, PSA, albumin, hemoglobin, or neutrophil or platelet counts, and results may be due to chance.

<sup>d</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>e</sup>Analysis includes 2 patients in the placebo group with no pain or analgesic use at baseline. A WHO ladder score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use.

<sup>f</sup>Log transformation was performed for baseline variables with heavily skewed distributions.

## Safety of Radium-223 in CRPC

**Supplemental Table 5** Multivariate Analysis of Grades 2-4 Anemia and Thrombocytopenia (Placebo, Safety Population; N = 301)

Baseline Variable	Anemia (N = 290)			Thrombocytopenia (N = 292)		
	OR	95% CI	P	OR	95% CI	P
Age (years) per 1-year increase <sup>a,b</sup>	0.95	0.92-0.99	.025	.090	0.83-0.98	.014
Prior docetaxel use (yes/no)	1.18	0.61-2.25	.624			
<b>Extent of Disease<sup>b</sup></b>						
6-20 metastases vs. <6 metastases	2.51	0.50-12.52	.263			
>20 metastases vs. <6 metastases	4.49	0.88-22.92	.071			
Superscan <sup>c</sup> vs. <6 metastases	6.21	1.06-36.29	.043			
Log baseline tALP per 10-fold increase <sup>d</sup>	3.43	1.38-8.53	.008			
Log baseline LDH per 10-fold increase <sup>b,d</sup>	0.34	0.09-1.27	.109			
Log baseline PSA per 10-fold increase <sup>b,d</sup>	1.39	0.82-2.36	.224	9.37	2.48-35.32	.001
Baseline hemoglobin <sup>b</sup> per 1 unit decrease	1.47	1.16-1.87	.001			
Baseline platelet <sup>b</sup> per 100 unit decrease	0.74	0.53-1.02	.069	1.33	0.64-2.75	.439

Based on a logistic regression model. Odds ratios of > 1 represent an increase in risk associated with an increase in baseline variable. Odds ratios are relative risk for 1 unit increase in baseline variable (for those without log transformation) or a 10-times increase (for those with log transformation). Analyses include adjustment for treatment effect.

Abbreviations: LDH = lactate dehydrogenase; N = number of patients included in the model; OR = odds ratio; PSA = prostate-specific antigen; tALP = total alkaline phosphatase.

<sup>a</sup>Relative increase in risk for an adverse event with respect to an increase in age of 1 year.

<sup>b</sup>ALSYMPCA was not randomized by, age, extent of disease, LDH, PSA, hemoglobin, or platelet counts, and results may be due to chance.

<sup>c</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>d</sup>Log transformation was performed for baseline variables with heavily skewed distributions.

**Supplemental Table 6** Stepwise Analysis of Grade 2-4 Anemia and Thrombocytopenia (Placebo, Safety Population; N = 301)

Baseline Variable	Anemia (N = 290)			Thrombocytopenia (N = 292)		
	OR	(95% CI)	P	OR	(95% CI)	P
Age (years) per 1-year increase <sup>a,b</sup>	0.95	0.91-0.99	.015	0.90	0.83-0.98	.014
<b>Extent of Disease<sup>b</sup></b>						
6-20 metastases vs. <6 metastases	2.67	0.56-12.85	.220			
>20 metastases vs. <6 metastases	5.20	1.06-25.48	.042			
Superscan <sup>c</sup> vs. <6 metastases	7.01	1.24-39.47	.027			
Log baseline tALP per 10-fold increase <sup>b,d</sup>	3.67	1.50-8.97	.004			
Log baseline LDH per 10-fold increase <sup>b,d</sup>	0.32	0.09-1.21	.094			
Log baseline PSA per 10-fold increase <sup>b,d</sup>				9.37	2.48-35.32	.001
Baseline hemoglobin <sup>b</sup> per 1 unit decrease	1.52	1.20-1.91	<.001			
Baseline platelet <sup>b</sup> per 100 unit decrease	0.77	0.56-1.06	.114	1.33	0.64-2.75	.439

Based on a logistic regression model. Odds ratios of > 1 represent an increase in risk associated with an increase in baseline variable. Odds ratios are relative risk for 1 unit increase in baseline variable (for those without log transformation) or a 10-times increase (for those with log transformation). Analyses include adjustment for treatment effect.

Abbreviations: LDH = lactate dehydrogenase; N = number of patients included in the model; OR = odds ratio; PSA = prostate-specific antigen; tALP = total alkaline phosphatase.

<sup>a</sup>Relative increase in risk for an adverse event with respect to an increase in age of 1 year.

<sup>b</sup>ALSYMPCA was not randomized by, age, extent of disease, LDH, PSA, hemoglobin, or platelet counts, and results may be due to chance.

<sup>c</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>d</sup>Log transformation was performed for baseline variables with heavily skewed distributions.

**Supplemental Table 7** Baseline Characteristics of Patients With Grade 3 or 4 Thrombocytopenia

Characteristic <sup>a</sup>	Radium-223 (N = 38)	Placebo (N = 6)
<b>Age</b>		
Median (range), years	68 (49-86)	66 (61-72)
>75 years, n (%)	7 (18)	0 (0)
<b>Race, n (%)</b>		
White	38 (100)	6 (100)
<b>tALP Level, n (%)</b>		
<220 U/L	17 (45)	3 (50)
≥220 U/L	21 (55)	3 (50)
<b>Current Use of Bisphosphonates at Study Entry, n (%)</b>		
Yes	21 (55)	1 (17)
No	17 (45)	5 (83)
<b>Prior Docetaxel Use, n (%)</b>		
Yes	31 (82)	5 (83)
No	7 (18)	1 (17)
<b>ECOG PS,<sup>b</sup> n (%)</b>		
0	10 (26)	1 (17)
1	24 (63)	3 (50)
≥2	4 (11)	2 (33)
<b>WHO Ladder for Cancer Pain</b>		
0-1 (no pain or mild pain; no opioid use)	14 (37)	2 (33)
2 (moderate pain; occasional opioid use)	8 (21)	3 (50)
3 (severe pain; regular daily opioid use)	16 (42)	1 (17)
<b>Extent of Disease, n (%)</b>		
<6 metastases	2 (5)	0
6-20 metastases	13 (34)	3 (50)
>20 metastases or superscan <sup>c</sup>	23 (61)	3 (50)
<b>EBRT Within 12 Weeks of Screening, n (%)</b>		
Yes	8 (21)	0
No	30 (79)	6 (100)
<b>Biochemical Values, Median (Range)<sup>d</sup></b>		
Albumin, g/L	38 (27-48)	39 (31-46)
tALP, U/L	252 (79-2681)	288 (112-758)
LDH, U/L	300 (184-1575)	410 (142-1301)
PSA, µg/L	344 (12-4955)	1472 (145-3500)
<b>Hematologic Values, Median (Range)<sup>d</sup></b>		
Hemoglobin, g/dL	11 (9-14)	12 (10-14)
Neutrophils (absolute), ×10 <sup>9</sup> /L	4 (2-10)	5 (3-10)
Platelets, ×10 <sup>9</sup> /L	229 (75-645)	173 (78-321)
Lymphocytes, ×10 <sup>9</sup> /L	1 (0.5-3)	2 (0.8-3)

**Supplemental Table 7** Continued

Characteristic <sup>a</sup>	Radium-223 (N = 38)	Placebo (N = 6)
Time since diagnosis of prostate cancer, months <sup>e</sup>	59 (10-173)	41 (17-64)
Time since diagnosis of bone metastases, months <sup>e</sup>	22 (8-83)	31 (17-64)

Abbreviations: EBRT = external beam radiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; tALP = total alkaline phosphatase; WHO = World Health Organization.

<sup>a</sup>Percentages may not sum to 100% due to rounding.

<sup>b</sup>Value recorded at screening.

<sup>c</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>d</sup>Value recorded at week 0. If this value was missing, then the value recorded at screening was used. The normal values were as follows: albumin, 36-45 g/L; total alkaline phosphatase, 35-105 U/L; lactate dehydrogenase, 115-225 U/L; prostate-specific antigen, 0-3.999 µg/L; hemoglobin, 13.4-17.0 g/dL; neutrophils (absolute), 2-7.5 × 10<sup>9</sup>/L; platelets, 150-350 × 10<sup>9</sup>/L; lymphocytes 1-4 × 10<sup>9</sup>/L.

<sup>e</sup>Calculated relative to randomization; 1 month is regarded as 30 days.

## Safety of Radium-223 in CRPC

**Supplemental Table 8** Demographics and Baseline Characteristics of Patients With Pancytopenia or Bone Marrow Failure Compared With ITT Population

Characteristic <sup>a</sup>	Pancytopenia Patients <sup>b</sup>	ITT Population	
	Radium-223 (N = 13)	Radium-223 (N = 614)	Placebo (N = 307)
<b>Age</b>			
Median (range), years	66 (57-78)	71 (49-90)	71 (44-94)
>75 years, n (%)	1 (8)	171 (28)	90 (29)
<b>Race, n (%)</b>			
White	13 (100)	575 (94)	290 (95)
<b>tALP Level, n (%)</b>			
<220 U/L	9 (69)	348 (57)	169 (55)
≥220 U/L	4 (31)	266 (43)	138 (45)
<b>Current Use of Bisphosphonates at Study Entry, n (%)</b>			
Yes	6 (46)	250 (41)	124 (40)
No	7 (54)	364 (59)	183 (60)
<b>Prior Docetaxel Use, n (%)</b>			
Yes	11 (85)	352 (57)	174 (57)
No	2 (15)	262 (43)	133 (43)
<b>ECOG PS,<sup>c</sup> n (%)</b>			
0	2 (15)	165 (27)	78 (26)
1	11 (85)	371 (61)	187 (61)
≥2	0	77 (13)	41 (13)
<b>WHO Ladder for Cancer Pain</b>			
0-1 (no pain or mild pain; no opioid use)	8 (62)	269 (44)	139 (45)
2 (moderate pain; occasional opioid use)	3 (23)	151 (25)	78 (25)
3 (severe pain; regular daily opioid use)	2 (15)	194 (32)	90 (29)
<b>Extent of Disease, n (%)</b>			
<6 metastases	0	100 (16)	38 (12)
6-20 metastases	7 (54)	262 (43)	147 (48)
≥20 metastases or superscan <sup>d</sup>	6 (46)	249 (41)	121 (39)
<b>EBRT Within 12 Weeks of Screening, n (%)</b>			
Yes	0	99 (16)	48 (16)
No	13 (100)	515 (84)	259 (84)
<b>Biochemical Values, Median (Range)<sup>e</sup></b>			
Albumin <sup>f</sup> , g/L	38 (29-43)	40 (24-53)	40 (23-50)
tALP, U/L	172 (56-1095)	211 (32-6431)	223 (29-4805)
LDH, U/L	283 (179-1199)	315 (76-2171)	336 (132-3856)
PSA, µg/L	334 (22-1045)	146 (4-6026)	173 (2-14,500)
<b>Hematologic Values, Median (Range)</b>			
Hemoglobin, g/dL	12.0 (9-15)	12.2 (9-16)	12.1 (9-16)
Neutrophils <sup>g</sup> (absolute), ×10 <sup>9</sup> /L	3.6 (2-7)	4.5 (1-17)	4.4 (1-12)
Platelets <sup>g</sup> , ×10 <sup>9</sup> /L	219 (115-498)	244 (69-645)	240 (51-580)
Lymphocytes <sup>g</sup> (absolute), ×10 <sup>9</sup> /L	1.1 (1-2)	1.3 (0.3-7)	1.4 (0.2-4)
Time since diagnosis of prostate cancer, months <sup>h</sup>	56 (10-135)	59 (8-313)	52 (1-347)
Time since diagnosis of bone metastases, months <sup>h</sup>	22 (0.3-89)	25 (0-254)	22 (0.2-183)

Abbreviations: EBRT = external beam radiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; ITT = intent to treat; PSA = prostate-specific antigen; tALP = total alkaline phosphatase; WHO = World Health Organization.

<sup>a</sup>Percentages may not sum to 100% due to rounding.

<sup>b</sup>Includes patients with the preferred term pancytopenia or bone marrow failure.

<sup>c</sup>Value recorded at screening.

<sup>d</sup>Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

<sup>e</sup>Value recorded at week 0. If this value was missing, then the value recorded at screening was used. Normal values were as follows: albumin, 36-45 g/L; tALP, 35-105 U/L; LDH, 115-225 U/L; PSA, 0-3.999 µg/L; hemoglobin, 13.4-17.0 g/dL; neutrophils (absolute), 2-7.5 × 10<sup>9</sup>/L; platelets, 150-350 × 10<sup>9</sup>/L; lymphocytes, 1-4 × 10<sup>9</sup>/L.

<sup>f</sup>Median (range) from 12 patients.

<sup>g</sup>Safety population.

<sup>h</sup>Calculated relative to randomization; 1 month is regarded as 30 days.



**Supplemental Table 9** Xofigo Prescribing Information: Recommended Absolute Neutrophil and Platelet Counts Before Administration of Radium-223 to Patients With Castration-Resistant Prostate Cancer and Symptomatic Bone Metastases

Injection	Neutrophils	Platelets
1	$\geq 1.5 \times 10^9/\text{L}$	$\geq 100 \times 10^9/\text{L}$
2-6	$\geq 1.0 \times 10^9/\text{L}$ <sup>a</sup>	$\geq 50 \times 10^9/\text{L}$ <sup>a</sup>

<sup>a</sup>If no recovery to these values within 6 to 8 weeks after the last administration of radium-223 despite supportive care, further treatment with radium-223 should be discontinued.